The search for causative environmental factors in inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD) has become a 'prototype disease' for chronic auto-inflammatory disorders with a polygenic background and important multifaceted environmental trigger components. The environmental factors contribute both to pathogenesis and disease flares. Thus, IBD is a disease par excellence to study the interactions between host genetics, environmental factors (such as infections or smoking) and 'in-vironmental' factors - for example, our intestinal microbiota. Longitudinal intercurrent events, including the impact of long-term medication on disease progression or stabilization, can exemplarily be studied in this disease group. Whilst alterations in the human genome coding relevant variant protein products have most likely not emerged significantly over the last 50 years, the incidence of Crohn's disease and ulcerative colitis has dramatically increased in Western countries and more recently in the Asia Pacific area. An interesting concept indicates that 'Western lifestyle factors' trigger chronic intestinal inflammation or disease flares in a genetically susceptible host. To understand the disease pathogenesis as well as triggers for flares or determinants of disease courses, we must further investigate potential en(in)vironmental factors. As environmental conditions, in contrast to genetic risk factors, can be influenced, knowledge on those risk factors becomes crucial to modulate disease incidence, disease course or clinical presentation. It is obvious that prevention of environmentally triggered disease flares would be a goal most relevant for IBD patients. An increased prevalence of IBD in urban environment has been documented in Switzerland by the Swiss IBD cohort study. Several studies have attempted to identify such factors; however, only a few have been validated. The best investigated environmental factor identified in IBD cohort analyses is smoking. Other environmental factors that have been associated with clinical presentation or risk of inflammatory flares as well as increased incidence are diet and food additives. The so-called 'hygiene hypothesis' suggests that increased hygiene in childhood associated with reduced exposure to pathogens may leave the mucosal immune system insufficiently trained and thus prone to uncontrolled inflammation. Oral contraceptives and non-steroidal anti-inflammatory drugs are the 2 main classes of frequently taken drugs that have been attributed to have the potential to cause flares of the disease. What is likely to be the connection between the genetic susceptibility and the environmental triggers? There is broad evidence for a critical role of the commensal enteric microbiota as a modulator of immunologic responses relevant during onset and chronification of IBD.

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The Search for Causative Environmental Factors in Inflammatory Bowel Disease

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Key Words
Inflammatory bowel disease · Pathophysiology · Environmental factors · Hygiene hypothesis

Abstract
Inflammatory bowel disease (IBD) has become a 'prototype disease' for chronic auto-inflammatory disorders with a polygenic background and important multifaceted environmental trigger components. The environmental factors contribute both to pathogenesis and disease flares. Thus, IBD is a disease par excellence to study the interactions between host genetics, environmental factors (such as infections or smoking) and 'in-vironmental' factors – for example, our intestinal microbiota. Longitudinal intercurrent events, including the impact of long-term medication on disease progression or stabilization, can exemplarily be studied in this disease group. Whilst alterations in the human genome coding relevant variant protein products have most likely not emerged significantly over the last 50 years, the incidence of Crohn's disease and ulcerative colitis has dramatically increased in Western countries and more recently in the Asia Pacific area. An interesting concept indicates that 'Western lifestyle factors' trigger chronic intestinal inflammation or disease flares in a genetically susceptible host. To understand the disease pathogenesis as well as triggers for flares or determinants of disease courses, we must further investigate potential en(in)vironmental factors. As environmental conditions, in contrast to genetic risk factors, can be influenced, knowledge on those risk factors becomes crucial to modulate disease incidence, disease course or clinical presentation. It is obvious that prevention of environmentally triggered disease flares would be a goal most relevant for IBD patients. An increased prevalence of IBD in urban environment has been documented in Switzerland by the Swiss IBD cohort study. Several studies have attempted to identify such factors; however, only a few have been validated. The best investigated environmental factor identified in IBD cohort analyses is smoking. Other environmental factors that have been associated with clinical presentation or risk of inflammatory flares as well as increased incidence are diet and food additives. The so-called 'hygiene hypothesis' suggests that increased hygiene in childhood associated with reduced exposure to pathogens may leave the mucosal immune system insufficiently trained and thus prone to uncontrolled inflammation. Oral contraceptives and non-steroidal anti-inflammatory drugs are the 2 main classes of frequently taken drugs that have been attributed to have the potential to cause flares of the disease. What is likely to be the connection between the genetic susceptibility and the environmental triggers? There is broad evidence for a critical role of the commensal enteric microbiota as a modulator of immunologic responses relevant during onset and chronification of IBD.

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Introduction

Inflammatory bowel disease (IBD) has become a prototype for a polygenetic disease that is associated with many genetic risk factors [1, 2]. For both ulcerative colitis (UC) and Crohn's disease (CD), in the meantime, more than 200 single nucleotide polymorphisms have been identified in large genome-wide association studies [3–8].

However, it is also clear that those genetic risk factors only partially contribute to the pathogenesis of IBD. Those 'genetic risk factors' are prevalent in our population since hundreds of years. Nevertheless, in Europe and the United States, the so-called westernized countries, the incidence and prevalence of IBD has increased in the last 100 years [9, 10]. More recently, both incidence and prevalence of not only UC but also IBD in general have increased in Asian countries such as China, Indonesia or India [11]. In addition to that, forecasts suggest that IBD is continuously on the rise in the next few years, especially within the developing world [12]. The recent increase in incidence clearly indicates that there must be environmental factors that contribute to the onset of IBD.

Most likely those causative environmental factors in IBD are associated with the changes of lifestyle and environmental conditions that could be observed during the last 100 years in Europe and the last 20–30 years in many Asian countries. This has led to the concept that the onset of IBD is associated with specific factors of the so-called westernized lifestyle. The findings have also contributed to the 'hygiene hypothesis' suggesting that the improvement in hygienic conditions and the reduction of so-called natural stimulation of the intestinal immune system are predisposing factors for the development of IBD [13–16]. Obviously, people living under worse hygienic conditions have a lower risk to develop IBD. Of course, one of the major obstacles in the search of predictive environmental factors is that it is very hard to identify a single factor that has changed during the last 100 years [1, 17]. Hygienic improvement is always associated with changes in household equipment such as refrigerators or change in environmental bacteria.

The Role of the Exposome: Onset of Disease or Disease Flares

It is now assumed that lifestyle and environmental factors in industrialized countries contribute up to 70% of the risk to develop IBD, whereas the genetic susceptibility is only responsible for about 30% of the disease incidence [1, 18–25]. On the other hand, it might well be that those environmental factors can mainly exert their influence in patients that have a certain genetic risk.

The environmental factors that might be causative for any disease are now summarized under the term 'exposome' (fig. 1) [1, 17, 26–30]. 'Exposome' refers to an umbrella term, subsuming all the factors an individual is exposed to during lifetime. Of course, the genetic susceptibility is not changed in an individual during the action of an exposome. However, the exposome and the 'infectome' as a part of the exposome (representing the potential pathogens in the environment) [31, 32] may either act on the microbiota composition of the gut or on the epigenetic imprinting of the cells of the intestinal mucosa [1].

It is very hard to identify causative exposomal factors as they permanently influence an individual long before the onset of a disease. In the case of a patient with CD who develops first symptoms at the age of 18 years, we have to assume that the exposome continuously influenced this person for the last 18 years (fig. 1). The specific hit that may have finally caused the onset of CD must not necessarily have occurred right before the first symptoms have appeared. There might be a subclinical inflammation of the intestinal mucosa that only becomes apparent when some destruction of the bowel wall has already happened [1]. In addition, there might be a histological inflammation even when no endoscopic inflammation is visible.

As there is a long period of time when exposomal factors act on an individual without visible consequence, it appears to be almost impossible to identify specific environmental factors that have a specific influence on onset of disease [1]. For obvious reasons it is much easier to identify exposomal and environmental factors that induce flares of UC or CD. Patients that suffer from IBD have already been identified and are closely followed up (e.g., in specific cohort projects such as the Swiss IBD Cohort Study, SIBDCS) [33]. In such cohort projects, specific triggers of flares can be identified. Environmental triggers of flares also might play a role for the onset of the disease and the basic pathophysiology of disease development. However, in those cases, the pathomechanisms behind those factors need to be elucidated and subsequently proven in basic research approaches.

Environmental Factors Known to Play a Role for Disease Flares

A number of factors have been identified that contribute to the risk of having a disease flare in a certain time period.

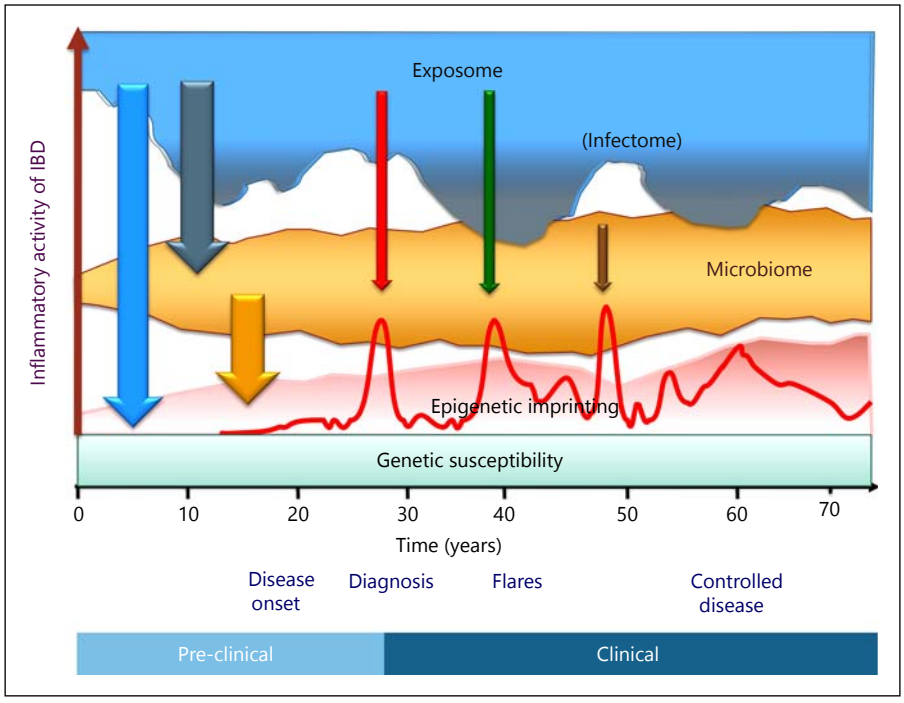

Fig. 1. Environmental factors (exposome, infectome and microbiota) that influence IBD onset and the risk of flares (modified according to [1]). The genetic susceptibility of a human remains constant during lifetime. In contrast, the exposome (blue arrow), the infectome – as part of the exposome – (grey arrow) and the microbiome (yellow arrow) permanently influence the function of the cells of the intestinal wall inducing epigenetic changes in those cells long before the onset of IBD. The exposome/infectome may either directly (blue arrow) cause epigenetic changes in an individual of via influences transmitted by microbiota changes (grey and yellow arrows). Certain exposomal/environmental factors may then trigger the onset of IBD (red arrow). Their identification remains a major challenge. It is easier to identify environmental factors (green) or microbiota factors (brown) that trigger disease flares. Ideally, those factors can be avoided leading to controlled disease.

- Among the risk factors for disease flares, in both CD and UC, are low vitamin D levels [34–39]. Surprisingly there is also an increased risk of vitamin D deficiency in UC [35, 37, 38, 40]. In patients with UC, the absorption of vitamin D should not be impaired as the inflammation only affects the large bowel. Nevertheless, the risk of a vitamin D deficiency is increased. In patients with vitamin D deficiency, in both CD and UC, the risk of having a flare is about 2-fold increased [41], whereas substitution in CD was shown to reduce relapse risk in quiescent CD [42]. Moreover, lower vitamin D serum levels were also revealed to be associated with an increased risk of colorectal cancer in IBD patients [43].
- There is still some controversy about non-steroidal anti-rheumatic drugs (NSARs) [44]. However, the reports that indicate an increased risk of having a flare of CD and UC upon treatment with NSARs are more consistent [45]. Overall risk (OR) between 1.6 and 1.9 is reported in a recent review [46, 47].
- Many investigations have focused on the impact of diet on a disease course in IBD [48–58]. Most consistently, it has been shown that a high intake of poly-unsaturated fatty acids as well as saturated fats, omega6 fatty acids and meat may increase the risk of having flares of CD or a more severe disease course.
- Whereas fibers and high fiber intake seem to be somewhat protective during remission and prevent flares of the disease [59]. During the presence of a disease flare, the intake of fibers is not beneficial [60].
- Interestingly, oral contraceptives in women increase the risk of having a flare of CD to more than 2 fold [18, 61–66]. The same is true for hormone substitution therapy in UC [18, 61–66]. Both factors indicate that hormonal influences also may play a role at least for the risk of disease flares.
- For breastfeeding, conflicting results have been reported [20, 67–71]. A meta-analysis could not conclusively decide whether there is a protective or even disease-aggravating effect [72]. If there is a protective effect at all it may be related to the duration of breastfeeding [73].
- Perhaps the best epidemiological evidence of a risk-modifying property of an environmental factor is available for cigarette smoking [74–77]. Cigarette smoking definitely is a risk factor for flares of CD and for perianal complications [78–81]. Smoking has a clear negative effect on the disease course [78–81]. On the other hand, smoking is protective and prevents flares in UC [78, 82]. The mechanisms behind that are unclear. However, our group could show that smoking sensation clearly changes the composition of the intestinal microbiota [74, 83]. The change in microbiota

composition reveals a more pro-inflammatory profile. Those data indicate that smoking could indeed influence colitis risk via an important influence on the composition of the intestinal bacteria.

- The quality of life of patients with IBD is improved and stress is reduced in patients with CD who engage in regular low intensive exercise [84, 85]. On the other hand, a long-term exercise with oxygen depletion may be deleterious and have contrary effects. Runner's colitis may not only be related to patients without IBD. This is indeed a risk for flares in patients with IBD.
- It is well known that anxiety and depressive symptoms also increase the risk of having a flare in the next 12 months [86, 87]. This has been nicely shown for CD [46]. Other authors indicate that the same is true for UC [88]. Also in the SIBDCS, anxiety was shown to be a relevant risk factor for disease flares [89].
- Hormonal replacement therapy may be a protective factor for postmenopausal female IBD patients [90].
- In a case–control study in pediatric patients, it has been shown that the presence of autoimmune diseases in the family is also a risk factor to develop IBD.
- Further protective factors were the number of siblings, the presence of pets and the present of a parasitosis in the family, all supporting the hygiene hypothesis.

Identification of Pathomechanisms

As mentioned above, in the case of environmental factors that can cause flares or may be responsible for onset of disease, the pathomechanisms have to be elucidated as a prerequisite to ultimately derive beneficial clinical impact for our patients. In a recent publication, we could identify a potential mechanism by which diet-derived nanoparticles can induce inflammasome activation and therefore contribute to intestinal inflammation [91]. One of those nanoparticles frequently used in the food industry is titanium dioxide, usually used as microparticles. However, in industrially produced microparticles, about 10% of the particles appear to be nanoparticles of about 100 nm of size. Those particles can penetrate cell membranes by physical interaction without needing a receptor. The total uptake of nanoparticles by patients is at an average of 2.5 mg per person and day but may increase up to 40 mg. Interestingly, there is a high content of titanium dioxide in coffee whitener, pastry (due to the flour content), toothpaste, chewing gum or drug preparations. We could demonstrate that titanium dioxide activates the immune system [91]. This activation is mainly mediated via a protein complex called the inflammasome. The inflammasome consists of 3 subunits. The effector subunit is caspase-1 that cleaves pro-interleukin 1β (IL-1β) and to the mature IL-1β and pro-IL-18 that can then be secreted. We found that in cell culture titanium dioxide was a strong activator of the inflammasome and subsequently induced IL-1β release [91]. In a mouse model, there was an aggravation of colitis induced by dextran sodium sulfate in the presence of titanium dioxide in the diet [91]. This effect was concentration dependent. In NALP3, this effect was absent in knockout mice that lack the receptor for inorganic nanoparticles [91]. Interestingly, in patients with active UC, we could measure increased titanium levels in the blood serum indicating that indeed in patients with active inflammation of the colon titanium dioxide is taken up into the body [91]. When it is taken up, it most likely also activates the inflammasome; however, we have not proven that directly in our manuscript. Similarly, other food additives may activate the immune system. Among those food additives may be aluminum as shown by Pineton de Chambrun et al. [92].

Another recently highlighted compound that is frequently used in the food industry is emulgators. A recent highly appreciated manuscript has shown that emulgators may aggravate colitis by probably reducing the mucus layer in the colon, which would then be a mechanism that impairs the barrier function of the intestine [93].

Microbiota, Antibiotics and IBD

There are a number of epidemiological studies that show that antibiotics may increase the risk of IBD. Hviid et al. [94] have shown in a Dutch registry that antibiotic use in childhood increases the risk of IBD. Especially the tetracycline class of antibiotics and particularly doxycycline use was shown by his group to be associated with the development of IBD, particularly CD [94]. A similar association for oral tetracycline use and IBD has been identified by Margolis et al. [95]. Bernstein et al. [96–99] in Canada also could demonstrate that there is an association between the use of antibiotics in the first year of life and pediatric IBD. By the same group, an association between the use of antibiotics and new diagnosis of CD and UC in the adult population was shown. The antibiotics usually had been prescribed 2–5 years before the diagnosis. A recent meta-analysis by Ungaro et al. [100] in Am J Gastroenterology summarized 12 studies that focused on the risk of having IBD after the use of antibiotics. The meta-analysis indicates an OR of 1.57 with high statistical significance indicating that indeed antibiotic use may later on cause IBD [100].

However, as always those results have to been interpreted with caution. We have all learned that IBD is associated with a defect in innate immunity and such a defect may also manifest in increased number of infections. Those infections then would request antibiotic treatment. So the increased use of antibiotics in patients who finally suffer from IBD may just indicate an increase in the predisposition to infections due to the impaired innate immunity. This would mean that antibiotic use is just a factor associated with IBD but not at all causative or pathophysiologically relevant. Likewise, it appears perfectly plausible, that antibiotic usage in childhood reflects a proxy for a general 'higher' living standard, as children associated to a higher social stratum may grow up in a 'high-hygiene environment', accompanied by a lower threshold for visits to a physician and thus higher exposure to antibiotics.

Antibiotics have been shown to cause a dysbiosis [101–103]. Similar dysbiosis has been found in many patients with IBD. However, this may not necessarily be negative. Metronidazole, which has some beneficial effects during acute phases of UC and also in patients with CD who suffer from fistulae, clearly reduces the diversity upon treatment as we have shown recently (unpublished data). Accordingly, simultaneously with reducing the microbial diversity, it exerts beneficial effects for IBD patients. This indicates that a reduction of diversity of the microflora may not always be a negative effect. We have to learn a lot more about the impact of the microbiota on the intestinal immune system before we are able to draw any conclusions.

Other Environmental Factors

A recent factor we recently identified within the Swiss IBD Cohort to potentially contribute to the risk of having flares of IBD is high altitude journeys of flights [104, 105]. In the population we studied, there was a significant association of high altitude journeys and flights with the risk of having a flare of IBD [104, 105]. The days spent on altitudes above 2,000 m were also associated with the risk of having a disease flare. The same was true for the distance of the airplane flights. Whereas short distance flights seem to have a lower risk, the risk associated with long-term flights was higher.

Another risk factor for IBD flares we recently identified in the SIBDCS is the presence of heat waves, which clearly revealed to induce IBD flares [106]. With a latency period, they also induced bacterial or viral gastroenteritis. However, as the flares of IBD appeared with less latency as compared to the gastroenteritis, it is highly unlikely that an antecedent infection reflected the actual trigger the flare of IBD. Obviously, there must be a pathogenetic mechanism by which the physiological stress course by a heat wave directly may trigger a flare of IBD [106].

Summary

As environmental changes that trigger disease flares or the onset of CD and UC are of utmost importance for our patients, we have to learn more about underlying mechanisms, for example, whether hypoxia is protective or causes flares of IBD. Situations of hypoxia can be avoided or can be prevented as many of the environmental factors.

Environmental factors and lifestyle factors, the so-called exposome, most likely contribute significantly to onset and disease course of IBD. Results from epidemiological studies for many of the lifestyle factors such as diet or breastfeeding are conflicting. One of the reasons for those conflicting data is the fact, that we frequently do not understand the underlying pathophysiological mechanisms, but instead just observe associations of those environmental factors with an increase in disease risk. Evidently, association is not equal to causality. Confounders may bias many of those studies, as for instance eluted to regarding antibiotics. Therefore, we are faced with a largely unmet need to identify the pathophysiological pathways at present that genuinely contribute to the impact of environmental factors on disease course.

Non-classical lifestyle factors such as hypoxia, travelling and climate may play an important role that has to be further investigated. The effects of those factors may either be mediated by the intestinal microbiota or directly via the innate immune system in epithelial cells or the mucosal immune system.

Disclosure Statement

The authors declare that they have nothing to disclose with respect to this article.

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